DECLARATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of: Takahiro ITO et al.
Serial No. 10/509,912: Group Art Unit: 1623
Filed: October 4, 2004: Examiner: Jonathan S Lau
For: LIQUID PREPARATION COMPRISING CAMPTOTHECIN DERIVATIVE AND PHARMACEUTICAL COMPOSITION PRODUCIBLE BY LYOPHILIZING THE PREPARATION

Honorable Commissioner for Patents
Sir:

[A] I, Dr. Takahiro ITO, a citizen of Japan, having an address of 10-1-412, Nishinomiyahama 4-come, Nishinomiya-shi, Hyogo-ken, Japan, declare and state as follows.

I am one of the co-inventors of the subject matter of the above-identified application and know well all aspect of the invention embodied therein.

I graduated from the faculty of pharmaceutical sciences of Kumamoto University, Japan, in 1989, and then completed the post graduate course of pharmaceutical sciences Kyushu University, Japan, in 1991. I was awarded the degree of Doctor of Philosophy in pharmaceutical sciences from Toho University in 2006.

I am a pharmacist and a member of Japan Pharmaceutical Association.

Since April, 1991, I have been an employee of Mitsubishi Tanabe Pharma Corporation (Former Tanabe Seiyaku Co. Ltd.), 2-10 Dosho-machi 3-chome, Chuo-ku, Osaka, Japan, and I am presently in Charge of manager of Marketed Drug regulatory Affairs Department of the company after working for 14 years as a researcher of Pharmaceutical Research Division, CMC Research Laboratory of the company.

[B] I read through the Office Action (Advisory Action) dated August 28, 2008 on the present patent application. In order to show that the present

invention is not expected by the cited references (Harada et al. reference and Wall et al. reference), following experiments was conducted by CMC Research Laboratory of the company under my supervision and the results are reported below.

Comparative Experiments

1. Method:

Two kinds of liquid preparations having formulations (ingredients) shown in the following Table 1 and Table 2 were prepared. Each preparation was preserved at 40℃ for 90 days, at 50℃ for 30 days and at 60℃ for 20 days, and then the residual rate (%) of the drug was measured. When the preparation is preserved at 25℃, term (days) which would be taken for the residual rate of the drug to become 90 % was calculated by using Arrhenius plot method.

Table 1

Formulation 1: A liquid preparation not containing sugar alcohol

Ingredient	Amount
Drug (same as in Example 1 of present invention)	0.400 g
Sodium chloride	0.771 g
Sodium dihydrogenphosphate	0.180 g
Citric acid	0.071 g
Total (pH)	100 mL (6.0)

Table 2

Formulation 2: A liquid preparation containing sugar alcohol

Ingredient	Amount
Drug (same as in Example 1 of present invention)	0.400 g
Sorbitol	4.283 g
Sodium dihydrogenphosphate	0.180 g
Citric acid	0.071 g
Total (pH)	100 mL (6.0)

2. Results:

The results are shown in following Table 3 and 4.

Table 3

Stability of the drug in preparation of formulation 1

Preservation temperature	Residual rate (%) Preservation term	Estimated days taken for residual rate to become 90%
60 ℃	91.9% (20 days)	29.7 days
50 ℃	94.2% (30 days)	79.6 days
40 ℃	94.5% (90 days)	227.0 days
25 ℃	----	1248.4 days (3.42 years)

E = 21.1 kcal, r = -0.997

Table 4

Stability of the drug in preparation of formulation 2

Preservation temperature	Residual rate (%) Preservation term	Estimated days taken for residual rate to become 90%
60 ℃	92.6% (20 days)	24.5 days
50 ℃	94.3% (30 days)	134.3 days
40 ℃	94.2% (90 days)	200.4 days
25 ℃	----	923.8 days (2.53 years)

E = 18.9 kcal, r = -0.996

3. Consideration:

From the above results, when the preparation is preserved at 25℃, term (estimated term) which is taken for the residual rate of the drug to become 90% was 2.53 years on formulation 2, and 3.42 years on formulation 1.

Therefore, it is clear that formulation 1 not containing sorbitol is practically far efficient preparation comparing with formulation 2.

[C] The undersigned declares further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United State Code and that such willful false statements may jeopardize the validity of the above-mentioned application or any patenting thereon.

This 10th day of November, 2008

Takahiro Ito

Takahiro ITO